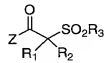
CLAIMS

1. A method of preparing alpha-sulfonyl derivatives of the formula V:



V

wherein Z is H, OH, -NYOX, $-OR_5$ or $-NR_5R_6$;

X is hydrogen, alkyl of 1-6 carbon atoms, benzyl, hydroxyethyl, t-butyldimethylsilyl, trimethylsilyl or tetrahydropyranyl;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_1 and R_2 are each, independently, hydrogen; aryl of 6 to 10 carbon atoms; 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S;

cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or R_1 and R_2 taken together with the carbon atom to which they are attached form a cycloalkyl ring of 3-8 carbon atoms or a 5-10 membered cycloheteroalkyl ring; and wherein the aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkyl, alkenyl, and alkynyl, may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$,

$-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_4 is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; $-C(O)_nR_5$, $-CONR_5R_6$ or SO_2R_5;

R_5 and R_6 are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R_5 and R_6 taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and

n is 1 or 2; or a pharmaceutical salt thereof,
which comprises reacting a sulfonyl fluoride of the formula III

$R_3'SO_2F$

III

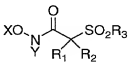
wherein R_3' is as hereinabove defined for R_3 with the proviso that R_3' does not contain a group that can form an anion under basic conditions; with a carbonyl compound of the formula IV:

IV

wherein Z is H, OH, YNOX, $-NR_5R_6$ or OR_5, and X, Y, R_1, R_2, R_5, and R_6 are as hereinabove defined; in the presence of a metal hydride or amide base in an ether

organic solvent at temperatures from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V;
any reactive substituent group(s) being protected during the reaction and removed thereafter ; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

2. A method as claimed in claim 1 in which the compound of formula (V) prepared wherein Z is H, OH, $-NR_5R_6$ or OR_5 is further reacted to convert it to an alpha-sulfonyl hydroxamic acid derivative of the formula I:

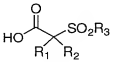


I

wherein X, Y, R_1, R_2 and R_3 are as defined in claim 1 or a pharmaceutically acceptable salt thereof; any reactive substituent group(s) being protected during the reaction and removed thereafter ; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

3. A method as claimed in Claim 2 wherein Z in the compound of formula V prepared is:
(i) OR_5 wherein R_5 is other than hydrogen and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out by:

a) reacting the compound of formula V with an alkali metal hydroxide in the presence of water, and/or ether organic solvent or alcohol at temperatures ranging from about 0°C to about 100°C to produce a carboxylic acid of the formula VI:



VI

wherein, R_1, R_2, and R_3 are as hereinabove defined; and

(b) reacting the carboxylic acid of formula VI with a hydroxylamine or hydroxylamine derivative of the formula VII:

XONHY

VII

wherein X and Y are as hereinabove defined; in the presence of suitable coupling reagent and polar organic solvent to produce a hydroxamate of the formula I

or

(ii) OH and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out according to step b) above.

4. The method of Claim 3 wherein the ether organic solvent in step a) is selected from tetrahydrofuran, diethylether and dioxane.

5. The method of Claim 3 wherein the alcohol in step a) is selected from methanol and ethanol.

6. The method of Claim 3 wherein the alkali metal hydroxide in step a) is selected from lithium hydroxide and sodium hydroxide.

7. The method of Claim 3 wherein the polar organic solvent in step b) is dimethylformamide.

8. The method of Claim 3 wherein the coupling reagent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride, N-hydroxybenzotriazole, N-methylmorpholine and oxalylchloride and triethylamine.

9. The method of Claim 3 wherein the coupling reaction is carried out at a temperature from about 0° C to 30° C.

10. The method of Claim 3 wherein the ether organic solvent used in the reaction between the compounds of formula III and IV is selected from tetrahydrofuran, diethylether and dioxane.

11. The method of Claim 3 wherein the metal hydride base or amide base used in the reaction between the compounds of formula III and IV and is selected from lithium diisopropylamine, lithiumhexamethyldisilazide, and sodium hydride.

12. The method of Claim 1wherein the sulfonyl fluoride of formula III is prepared by reacting a sulfonyl chloride of the formula II

$$R_3'SO_2Cl$$

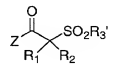
II

wherein R_3' is as defined for R_3 in claim 1 with the proviso that R_3' does not contain a group that can form an anion under basic conditions, with a fluorinating agent in the presence of a polar organic solvent from about 15°C to about 30°C.

13. The method of Claim 12 wherein the fluorinating agent is selected from potassium fluoride, potassium fluoride-calcium fluoride mixture and cesium fluoride.

14. The method of Claim 12 wherein the polar organic solvent is selected from acetonitrile and tetrahydrofuran.

15. A method of preparing alpha-sulfonyl derivatives of the formula V:



V

wherein wherein Z is H, OH, -NYOX, $-OR_5$ or $-NR_5R_6$;

R_1 and R_2 are each, independently, hydrogen; aryl of 6 to 10 carbon atoms; 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or R_1 and R_2 taken together with the carbon atom to which they are attached form a cycloalkyl ring of 3-8 carbon atoms or a 5-10 membered cycloheteroalkyl ring; and wherein the aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkyl, alkenyl, and alkynyl, may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3' is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl; provided that R_3' does not contain a group that can form an anion under basic conditions;

or a pharmaceutically acceptable salt thereof, which comprises the steps of :

a) reacting a sulfonyl fluoride of formula III:

$R_3'SO_2F$

III

wherein R_3' is as defined in claim 1; with an enol ether of formula VIII:

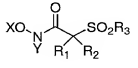
VIII

wherein Z is H, OH, YNOX, OR_5, $-NR_5R_6$ and R_1 and R_2, are as defined in claim 1; and

R_7 is cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or $-SiR_8R_9R_{10}$;

R_8, R_9, and R_{10} are each, independently, aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds; or two of R_8, R_9, and R_{10} taken together with the silicon atom to which they are attached form a heterocyclic ring of 5 or 6 members;
in the presence of a Lewis acid or fluoride reagent in an ether organic solvent at temperatures ranging from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V; any reactive substituent group(s) being protected during the reaction and removed thereafter ; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

16. The method of claim 15 in which the compound of formula (V) prepared wherein Z is H, OH, $-NR_5R_6$ or $-OR_5$ is further reacted to convert it to an alpha-sulfonyl hydroxamic acid derivative of the formula I:

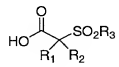


I

wherein X, Y, R_1, R_2 and R_3 are as defined in claim 1 or a pharmaceutically acceptable salt thereof; any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

17. The method of Claim 16 wherein Z in the compound of formula V prepared is:
(i) OR_5 wherein R_5 is other than hydrogen and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out by:

a) reacting the compound of formula V with an alkali metal hydroxide in the presence of water, and/or ether organic solvent or alcohol at temperatures ranging from about 0°C to about 100°C to produce a carboxylic acid of the formula VI:



VI

wherein, R_1, R_2, and R_3 are as hereinabove defined; and

(b) reacting the carboxylic acid of formula VI with a hydroxylamine or hydroxylamine derivative of the formula VII:

XONHY

VII

wherein X and Y are as hereinabove defined; in the presence of suitable coupling reagent and polar organic solvent to produce a hydroxamate of the formula I

or

(ii) OH and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out according to step b) above.

18. The method of Claim 17 wherein the ether organic solvent in step a) is selected from tetrahydrofuran, diethylether and dioxane.

19. The method of Claim 17 wherein the alcohol in step a) is selected from methanol and ethanol.

20. The method of Claim 17 wherein the alkali metal hydroxide in step a) is selected from lithium hydroxide and sodium hydroxide.

21. The method of Claim 17 wherein the polar organic solvent in step b) is dimethylformamide.

22. The method of Claim 17 wherein the coupling reagent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride, N-hydroxybenzotriazole, N-methylmorpholine and oxalylchloride and triethylamine.

23. The method of Claim 17 wherein the coupling reaction is carried out at a temperature from about 0° C to 30° C.

24. The method of claim 15 wherein the Lewis acid or fluoride reagent is selected from boron tribromide, tetrabutyl ammonium fluoride and sodium fluoride.

25. The method of Claim 24 wherein the ether organic solvent is selected from tetrahydrofuran, diethylether and dioxane.

26. The method of Claim 15 in which the sulfonyl fluoride of formula III is prepared by reacting a sulfonyl chloride of formula II

$R_3'SO_2Cl$

II

wherein R_3' is as hereinabove defined for R_3 with the proviso that R_3' does not contain a group that can form an anion under basic conditions, with a fluorinating agent in the presence of a polar organic solvent at from about 15°C to about 30°C to produce a sulfonyl fluoride of the formula III.

27. The method of Claim 26 wherein the fluorinating agent is selected from the group consisting of potassium fluoride, potassium fluoride-calcium fluoride mixture, and cesium fluoride.

28. The method of Claim 26 wherein the polar organic solvent is selected from acetonitrile or tetrahydrofuran.

29. The method of Claim 1 wherein X is H or lower alkyl of 1-6 carbon atoms.

30 The method of Claim 1 wherein Y is H.

31 The method of Claim 1 where Z is OH or OR_5 where R_5 is C_1-C_6 alkyl.

32. The method of Claim 1 wherein R_1 and R_2 together form a 5-10 membered cycloheteroalkyl ring containing 1-3 heteroatoms selected from N, NR_4, O and S wherein R_4 is as defined in Claim 1.

33. The method of Claim 32 wherein the cycloheteroalkyl ring is saturated.

34. The method of Claim 32 wherein the cycloheteroalkyl ring is has 6 atoms.

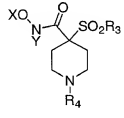
35. The method of Claim 32 wherein the heteroatom is NR_4 and R_4 is hydrogen, trifluoromethylsulfonyl, optionally substituted aralkyl of 7-10 carbon atoms, (C_6-C_{10}-aryl)carbonyl-, cycloheteroalkyl-carbonyl or heteroaryl-carbonyl.

36. The method of Claim 1 wherein R_3 is an optionally substituted C_6-C_{10} aryl group.

37. The method of Claim 1 wherein R_3 is a phenyl group substituted by one or more OR_5 groups.

38. The method of Claim 1 wherein R_5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or halophenyl.

39 The method Claim 1 in which the compound prepared is an alpha-sulfonyl hydroxamic acid derivatives of the general formula IA:

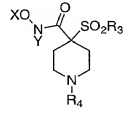


IA

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms; and Y, R_3 and R_4 are as defined in Claim 1 or a pharmaceutically acceptable salt thereof;

40. A method of preparing alpha-sulfonyl hydroxamic acid derivatives of the general formula IA:

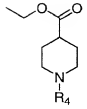


IA

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms; and Y, R_3 and R_4 are as defined in Claim 1 or a pharmaceutically acceptable salt thereof;
which comprises:

a) treating a compound of formula

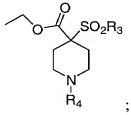


with diisopropylamide or lithium hexamethyldisilazide to form an enolate;

b) reacting the enolate with a sulfonyl fluoride:

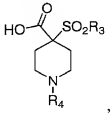
R_3SO_2F

to form a compound



;

c) hydrolyzing the compound of step b) to produce



, and

d) reacting compound of step c) with hydroxylamine or hydroxylamine derivative of the formula:

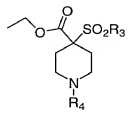
XONHY

in the presence of coupling reagent and polar organic solvent at temperatures ranging from about 0°C to about 30°C; and if desired isolating as a pharmaceutically acceptable salt.

41. The method of Claim 40 wherein the coupling reagent is selected from 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride, N-hydroxybenzotriazole, N-methylmorpholine and oxalylchloride and triethylamine.

42. The method of Claim 41 wherein the polar organic solvent is dimethylformamide.

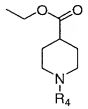
43. A method of preparing a compound of the formula



wherein

R_3 and R_4 are as defined in claim 1 or a pharmaceutically acceptable salt thereof, which comprises the steps of :

a) treating a compound of formula

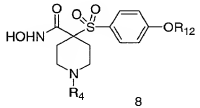


with diisopropylamide or lithium hexamethyldisilazide to form an enolate; and

b) reacting the enolate with a sulfonyl fluoride of formula:

R_3SO_2F.

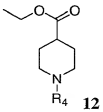
44. A method of preparing a compound of Formula **8**



8

wherein R_4 is as defined in claim 1 and R_{12} is methyl, n-butyl, 2-butynyl, or p-chlorophenyl; and n is 1 or 2; or a pharmaceutically acceptable salt thereof, which comprises the steps of :

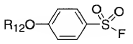
a) treating a compound of formula **12**



12

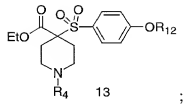
with diisopropylamide or lithium hexamethyldisilazide to form an enolate;

b) reacting the enolate with a sulfonyl fluoride of Formula **2**:



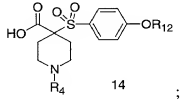
2 ;

to form a compound of Formula **13**



13 ;

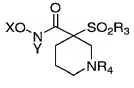
c) hydrolyzing compound of Formula **13** with lithium hydroxide to produce compound of Formula **14**



14 ; and

d) treating the compound of Formula **14** with oxalyl chloride, triethylamine, and hydroxylamine hydrochloride at temperatures ranging from about 0° to about 30°C.

45. A compound of Formula IX



IX

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having

from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

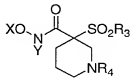
R_4 is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; $-C(O)_nR_5$, $-CONR_5R_6$ or SO_2R_5;

R_5 and R_6 are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R_5 and R_6 taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and

n is 1 or 2; or an optical isomer thereof or a pharmaceutically acceptable salt thereof.

46. A compound according to Claim 45 which is 1-benzyl-3-(4-methoxy-benzenesulfonyl)piperidine-3-carboxylic acid hydroxamide.

47. A pharmaceutical composition comprising a compound of Formula IX



IX

as defined in claim 45 or claim 46 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

48. A method of inhibiting pathological changes mediated by TNF-alpha converting enzymes (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 45, or a pharmaceutically acceptable salt thereof.

49. The method of Claim 48 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous sytem, inflammatory bowel disease or HIV infection.

50. A method of inhibiting pathological changes mediated by matrix metalloproteinases in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 45, or a pharmaceutically acceptable salt thereof.

51. The method of Claim 50 wherein the condition treated is age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

52. The method of Claim 50 wherein the condition treated is atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, or periodontal disease.